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HUMAN LEUCOCYTE ANTIGEN PHENOTYPES AND GOLD-INDUCED REMISSIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS

S. TEN WOLDE,* B. A. C. DIJKMANS,* J. J. VAN ROOD,† F. H. J. CLAAS,†
R. R. P. DE VRIES,† J. M. W. HAZES,* P. L. C. M. VAN RIEL,‡ A. VAN GESTEL‡
and F. C. BREEDVELD*

*Department of Rheumatology; †Department of Immunohaematology and Blood Bank, University Hospital Leiden, Leiden and ‡Department of Rheumatology, University Hospital Nijmegen, Nijmegen, The Netherlands

SUMMARY

To assess possible associations between human leucocyte antigens (HLA) and the achievement of remission during gold treatment, HLA typing was performed in 67 rheumatoid arthritis (RA) patients with a gold-induced remission and in 25 control RA patients who discontinued gold therapy because of lack of efficacy. Both groups of RA patients showed a significantly higher frequency of DR4 antigen and lower frequency of DR6 than a control population. There were no significant differences in HLA antigens between remission-responders and non-responders. It is concluded that HLA typing is not helpful in predicting the therapeutic response to parenteral gold therapy.

KEY WORDS: Human leucocyte antigens, Rheumatoid arthritis, Gold-induced remission.

GOLD salts have been used in the treatment of patients with rheumatoid arthritis (RA) for more than 60 yr [1] and are still considered as important disease-modifying anti-rheumatic drugs (DMARDs). Controlled studies have demonstrated that gold salts suppress the rheumatic process in 50–70% of RA patients [2–4] and induce remission in approximately 20% of the patients [5, 6]. Side-effects to gold requiring drug withdrawal occur in about one-third of patients [7]. Therefore the availability of clinical parameters likely to predict successful treatment with gold salts would be of interest.

The majority of studies attempting to identify factors which predict the response to gold have focused on association between human leucocyte antigens (HLA) and gold toxicity [8–13]. The most consistent association found in these studies was the association between gold toxicity and HLA-DR3. The results of studies that focused on associations between HLA antigens and beneficial therapeutic response to gold salts [10, 10–19] are inconsistent.

To investigate associations between HLA antigens and therapeutic response to parenteral gold we studied HLA phenotypes in a group of RA patients with a long-term remission during gold therapy and a control group of RA patients who had discontinued gold because of a lack of efficacy.

PATIENTS AND METHODS

Patients

Two groups of parenteral gold-treated patients with classical or definite RA according to 1958 American

Rheumatism Association (ARA) criteria [20] were chosen on the basis of their therapeutic response to gold (aurothioglucose in oil). The 67 patients with a gold-induced remission, designated remission-responders, fulfilled the preliminary remission-criteria of the ARA [21]. They were all seen by one investigator (SW) in eight rheumatology practices in The Netherlands (Leiden, Alkmaar, Haarlem, Dordrecht, Rotterdam, Gouda, Enschede and Almelo) between 1991 and 1993 and were treated with parenteral gold for at least 2 yr. None of the patients developed side-effects requiring drug withdrawal.

Since there were not enough patients who stopped gold because of a lack of efficacy with detailed prospective follow-up data in this source population, control patients were selected from a prospective study of RA patients as previously reported [22, 23]. This study included patients who had met the following criteria: classical or definite RA [20], disease duration shorter than 1 yr on entry to the study, and not previously treated with DMARDs. At the time of patient selection for the present study 192 patients had been included with a mean follow-up duration of 3.9 yr, of whom 74 had received parenteral gold. For this study all 25 patients were selected who discontinued parenteral gold therapy within the first 2 yr of treatment because of a lack of efficacy. These patients were designated as 'non-responders'. Patients who discontinued gold because of both lack of efficacy and gold toxicity were excluded from the study.

Since index and control patients were derived from two different source populations HLA frequencies of currently gold-treated patients at the University Hospital Leiden were compared with all gold-treated patients included in the prospective follow-up study from which the control patients were selected. This yielded no significant differences (data not shown).

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Correspondence to: S. ten Wolde, Department of Rheumatology, University Hospital Leiden, Building 1, C4-R, P.O. Box 9600, 2300 RC Leiden, The Netherlands.

The following data were collected from all patients: gender, age at the start of gold therapy, duration of gold therapy, serum levels of IgM-rheumatoid factor (RF) and HLA-A, B, C and DR typing. HLA frequencies of 505 randomly selected healthy Dutch blood transfusion donors served as a population control group.

HLA typing and statistical analysis

HLA-A, B and C, antigens were determined with a standard NIH microlymphocytotoxicity assay and HLA-DR antigen typing was done using a two-colour fluorescence test using a set of allo-antisera [24].

Significance testing was done using the chi-square test with Yates continuity correction, *t*-test for groups or Mann-Whitney test. When necessary, *P*-values were corrected for the Bonferroni inequality by multiplying them by the number of HLA-A, B or DR specificities tested (*P*_c). Odds ratios (OR) and their 95% confidence intervals (CI) were calculated for the associations between HLA typing and response to gold.

RESULTS

Clinical data of the two groups of RA patients are shown in Table I. The male percentage was higher among the remission-responders than among the non-responders, but this difference was not significant. The mean age at the start of gold therapy and the percentage RF positive patients were approximately the same in both groups. The disease duration at the start of gold therapy was significantly longer in the remission-responders compared to the non-responders, which can be ascribed to the policy for earlier treatment with DMARDs in the disease course in the source population of the control group. The frequency distributions of HLA-A, and DR of both groups of RA patients and of healthy Dutch blood donors are shown in Table II. Comparison of HLA frequencies between the two groups of parenteral gold-treated RA patients yielded no significant differences after correction for multiple

TABLE I
Clinical data of patients with RA with different therapeutic responses to parenteral gold

	Therapeutic response to parenteral gold		<i>P</i> -values*
	Remission (<i>N</i> = 67)	No response (<i>N</i> = 25)	
Male (%)	46	24	0.09
Rheumatoid factor positive (%)	79	84	0.82
Age at start gold therapy (yr)†	53.4 (12.2)	56.5 (12.1)	0.27
Time between diagnosis of RA and start of gold therapy (yr)‡	3.0 (0–40)	1.0 (0–4)	0.01
Duration of gold therapy (yr)‡	6.0 (2–27)	0.05 (0.5–2)	0.00

**P*-values using chi-square test with Yates correction, *t*-test or Mann-Whitney test.

†Mean (s.d.).

‡Median (range).

TABLE II
Frequency distributions of HLA antigens in two groups of patients with rheumatoid arthritis according to their therapeutic response to parenteral gold and of a control group of healthy Dutch blood donors

HLA	Therapeutic response to parenteral gold		Healthy blood donors (<i>N</i> = 505)
	Remission (<i>N</i> = 67)	No response (<i>N</i> = 25)	
A1	27	12	32
A2	63	52	48
A3	34	16	33
A9	13	36	19
A10	9	4	5
A11	12	4	12
A19	21	44	22
A28	4	8	9
B5	19	12	10
B7	24	16	30
B8	24	24	23
B12	31	12	24
B13	4	8	4
B15	12	36	16
B16	7	8	7
B17	7	12	8
B18	3	4	7
B21	1	0	2
B22	7	0	4
B27	10	12	5
B35	13	16	19
B37	4	0	6
B40	19	24	17
B41	1	0	2
DR1	31	28	21
DR2	25	16	29
DR3	15	20	25
DR4	66*	64*	28
DR5	10	12	18
DR6	12*	12	29
DR7	10	20	22
DR8	3	12	5
DR9	1	0	4
DR10	9	0	5

**P*_c-value <0.05 compared with healthy blood donors.

testing. Furthermore, there was no difference in the percentage of patients with homozygosity for DR antigens between remission-responders and non-responders.

As expected, the HLA-DR4 frequency was significantly increased in both groups of RA patients compared to the healthy blood donors (remission-responders *vs* controls: OR 4.95; 95% CI 2.88–8.49; and non-responders *vs* controls: OR 4.60; 95% CI 1.99–10.6). All other HLA frequencies of both groups of RA patients were not significantly different from the healthy blood donors after correction of the *P*-values for multiple testing, except for HLA-DR6 which was decreased in both groups.

DISCUSSION

The main conclusion of this study is the absence of a significant association between HLA antigens and therapeutic response to parenteral gold.

Earlier studies reported an increased frequency of HLA-DR3 in patients with a beneficial therapeutic

response to gold [10, 14, 15]. However, gold-induced proteinuria [9–11, 13, 25–28], thrombocytopenia [8, 25] and dermatitis [10, 13, 27, 29] have also been reported to be associated with HLA-DR3. Moreover, side-effects were reported to occur more frequently in responders compared with non-responders in several studies on gold-treated RA patients [10, 14, 30]. Therefore, it is conceivable that the previous reported association between HLA-DR3 and beneficial therapeutic responses to gold could be ascribed to the inclusion of patients with gold toxicity. The present study included patients with a gold-induced remission who were treated with parenteral gold for at least 2 yr without developing side-effects requiring drug withdrawal. This might explain the rather low frequency of HLA-DR3 observed in the remission-responders in this study. In contrast with previous reports the present study included a large sample size of RA patients with a gold-induced remission. Therefore, the statistical power of this study to find the previously reported increased HLA-DR3 frequency in 'excellent responders' [10] compared with non-responders was therefore at least 95%.

Although HLA antigens were equally distributed between the two groups of RA patients, the distribution of an other genetic factor, gender, tended to be different between remission-responders and non-responders to gold. The high male percentage observed in the remission group is in concordance with other studies [5, 14]. However, in the literature there is no support for the suggestion of disparity between the sexes in response to treatment with gold or other DMARDs [16, 31, 32]. Therefore, instead of a difference in response to gold the high male percentage possibly reflects the conclusions of several studies that men with RA fare better than women with RA [33, 34].

In conclusion, no associations were observed between HLA antigens and therapeutic response to parenteral gold therapy. Therefore, serological HLA typing will not be helpful in predicting a gold-induced remission. Non-HLA linked genetic variations in metabolic pathways may be more promising in predicting responses to drugs [35].

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